Influence of Moderate Physical Exercise on Insulin-Mediated and Non–Insulin-Mediated Glucose Uptake in Healthy Subjects

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To establish the relative importance of insulin sensitivity and glucose effectiveness during exercise using Bergman's minimal model, 12 nontrained healthy subjects were studied at rest and during 95 minutes of moderate exercise (50% maximum oxygen consumption [$\dot{V}o_2max$]). Each subject underwent two frequently sampled intravenous glucose tolerance tests (FSIGTs) for 90 minutes, at rest (FSIGTr) and during exercise (FSIGTe). Plasma glucose, insulin, and C-peptide were determined. Insulin sensitivity (S_I), glucose effectiveness at basal insulin (S_G), insulin action [X(t)], and first-phase (Φ_1) and second-phase (Φ_2) β-cell responsiveness to glucose were estimated using both minimal models of glucose disposal (MMg) and insulin kinetics (MMi). Glucose effectiveness at zero insulin (GEZI), glucose tolerance index (K_G), and the area under the insulin curve ($AUC_{0\text{-}90}$) were also calculated. Intravenous glucose tolerance improved significantly during physical exercise. During exercise, S_I (FSIGTr *v* FSIGTe: 8.5 ± 1.0 *v* 25.5 ± 7.2 × 10^{-5} · min^{-1} [pmol · L^{-1}]$^{-1}$, $P < .01$), S_G (0.195 ± 0.03 *v* 0.283 ± 0.03 × 10^{-1} · min^{-1}, $P < .05$), and GEZI (0.190 ± 0.03 *v* 0.269 ± 0.04 × 10^{-1} · min^{-1}, $P < .05$) increased; however, no changes in Φ_1 and Φ_2 were found. Despite a significant decrease in the insulin response to glucose ($AUC_{0\text{-}90}$, 21,000 ± 2,008 *v* 14,340 ± 2,596 pmol · L^{-1} · min, $P < .01$), insulin action [X(t)] was significantly higher during the FSIGTe. These results show that physical exercise improves mainly insulin sensitivity, and to a lesser degree, glucose effectiveness. During exercise, the insulin response to glucose was lower than at rest, but β-cell responsiveness to glucose did not change.

IN THE WHOLE BODY, glucose uptake is dependent on two mechanisms, insulin-mediated (IMGU) and non–insulin-mediated (NIMGU).[1] The first one takes place only in insulin-dependent tissues (muscle and fat), and the second occurs in both non–insulin-dependent (central nervous system, peripheral nerves, endothelial cells, and red and white blood cells) and insulin-dependent[2,3] tissues. These mechanisms are independently regulated.[4,5] At rest, glucose uptake takes place mainly (70%) in non–insulin-dependent tissues.[1,6] However, during physical exercise, muscle glucose uptake increases,[6,7] whereas it does not change in non–insulin-dependent tissues[7]; concurrently, insulin secretion decreases,[8,9] catecholamine secretion increases,[10] and euglycemia is maintained because hepatic glucose output (HGO) increases.[6,7,10] Although some in vitro[11-13] and in vivo[14] studies have demonstrated that insulin is not necessary for glucose uptake to increase during exercise, other studies in dogs and humans[15-17] have shown that this hormone plays an important role in glucose disposal during physical activity.

Many studies have dealt with the features of glucose uptake during exercise,[7,15,18-21] but only a few have tried to establish the relative importance of both IMGU and NIMGU.[14,17,22,23]

The main problem with this type of study is that usually two glucose clamps are necessary to quantify both IMGU and NIMGU: a hyperinsulinemic clamp to calculate whole-body glucose disposal, and another glucose clamp with a constant infusion of somatostatin to inhibit insulin secretion, which allows estimation of non–insulin-dependent glucose uptake. IMGU will be the difference between the glucose rate of disposal and NIMGU.[1] However, these methods are complex and expensive. The minimal model of glucose metabolism (MMg) affords us an easier approach to both IMGU and NIMGU calculation. This method provides both insulin sensitivity (S_L) and glucose effectiveness at basal insulin (S_G) indices from a simple intravenous glucose tolerance test.[24,25] The S_G index includes two components, basal insulin effectiveness (BIE) and glucose effectiveness at zero insulin (GEZI).[26] The last component represents the effect of glucose in promoting its own disposal independently of insulin.

Even though some studies have used the minimal model in exercise physiology,[22,27-30] to the best of our knowledge, none have applied this technique during exercise. The aim of our study was to determine the effect of acute physical exercise on minimal model parameters and to establish the relative importance of both the S_I index and GEZI during moderate physical exercise.

SUBJECTS AND METHODS

Subjects

Twelve healthy, non-obese (body mass index < 27 kg/m^2) subjects aged 20 to 61 years were studied. None of them had a family history of diabetes or hypertension or were taking any drugs that could alter carbohydrate tolerance, and none had a history of cardiac, renal, or liver disease. The physical activity of the subjects was variable, although no one was in competition training, and their life-style was sedentary. The study was approved by the Central Oxford Research Ethics Committee, and written consent was provided by all of the subjects.

Protocol

Each subject underwent two frequently sampled intravenous glucose tolerance tests (FSIGTs) for 90 minutes. This abbreviated protocol using tolbutamide was previously validated.[31] One of the tests, at rest, was used as a control (FSIGTr). The other one (FSIGTe) started 5 minutes after ergometric exercise began. There was at least 1 week

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between the two tests, and both were performed randomly. All of the subjects were instructed not to exercise the day before and to avoid intensive physical activity on the morning before testing.

FSIGTr

Subjects were consuming a weight-maintaining diet containing at least 300 g/d carbohydrate for 3 days before the study. Each subject came to our Unit at 8:30 AM after a 10- to 12-hour overnight fast. With the subject sitting, a dorsal hand vein was retrogradely cannulated with a 20-gauge catheter (Venflon 2; Viggo-Spectramed, Ohmeda, Sweden) and the hand was placed in a thermoregulated box maintained at 70°C to permit sampling of arterialized blood for determination of plasma insulin, glucose, and C-peptide concentrations. An antecubital vein from the contralateral arm was cannulated (Arterial cannula; Viggo-Spectramed) for glucose injection, and patency of the catheters was maintained with isotonic saline 0.9% NaCl infusion through a peristaltic pump (50 mL/h, Infusomat II; Braun, Melsungen, Germany). Basal samples were drawn at −15, −10, −5, and −1 minutes. At 0 minutes, glucose (11.4 g/m^2, dextrose 50% wt/vol) was injected over 2 minutes. Blood samples (4 mL) for glucose and insulin assay were taken according to the following sampling schedule at: 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 19, 22, 25, 27, 32, 36, 40, 44, 48, 52, 56, 60, 65, 70, 80, and 90 minutes, for a total of 26 postinjection samples. Blood samples were taken for measurement of C-peptide levels less frequently at −15, −10, −5, −1, 2, 5, 10, 25, 36, 60, and 90 minutes.

Collected samples were placed in heparinized syringes (Monovettes; Sarsted, Leicester, UK). All samples were kept on ice until centrifugation at 1,500 × *g* for 10 minutes at 4°C. Glucose was immediately determined, and the other plasma aliquots were frozen at −20°C for subsequent determination of insulin and C-peptide.

FSIGTe

Glucose injection took place 5 minutes after physical exercise began; the rest of the test was identical to the FSIGTr. Basal values for glucose, insulin, and C-peptide corresponded to the samples at −15 and −10 minutes.

Physical Exercise

Subjects were studied during upright continuous bicycle exercise for 95 minutes starting 5 minutes before glucose injection, at a work load to 50% of maximal aerobic capacity ($\dot{V}O_2$max). The blood pressure and electrocardiogram (ECG) were recorded during exercise. The exercise could be stopped because of physical exhaustion or if blood pressure values and/or ECG characteristics made it advisable.

The $\dot{V}O_2$max for each subject was determined at least 1 week before the first FSIGT to prevent the influence of previous exercise on glucose tolerance. The subject underwent a period of standard exercise testing on a bicycle ergometer (Ergomed 740; Siemens, Darmstadt, Germany) with continuous ECG and blood pressure monitoring. The test commenced at a load of 30W with increments of 15W every minute while maintaining a speed of 60 rpm until subjective exhaustion. The subjects breathed room air through a small Rudolph valve (Gallenkamp International, Loughborough, UK) that had a dead space of 16 L. Inspiratory volume was measured with a Parkinson-Cowan dry gas meter (Beckman Instruments, Fullerton, CA). Expired air was passed through a mixing chamber, where it was analyzed for oxygen and carbon dioxide content with a Servomex 540A paramagnetic oxygen analyzer (Beckman Instruments; accuracy, ±0.02%) and a Gould Mark IV infrared capnograph (PK Morgan, Kent, UK; accuracy, ±0.05%), respectively, to calculate $\dot{V}O_2$max.[32] The gas analyzers were calibrated before and after each test with three gases of known composition.

MMg

Bergman's minimal model was used to calculate both insulin sensitivity (S_L) and glucose effectiveness (S_G) indices.[24,33] Briefly, MMg is a mathematical representation of the kinetics of glucose during a FSIGT. The model is represented by two nonlinear, first-degree differential equations. The paramenters of the model were estimated using a nonlinear least-squares technique with a personal computer program (STELLUM-MMg) written in FORTRAN 77.[34,35] The same zero-weighting scheme for the early part (8 minutes) of the plasma glucose pattern was used in all of the cases studied. Once the model parameters have been estimated, it is possible to calculate both S_I and S_G indices.[24,25,33] To ensure maximal reliability of the indices, they were calculated as follows.[31] A computer-derived and predicted glucose value was used together with the actual fasting insulin value as the 180-minute values in the program. The predicted 180-minute glucose value was obtained by inserting the baseline glucose concentration as if it were the actual 180-minute data. The program provides expected glucose values for all time points. The basal insulin component of S_G is BIE, calculated as the product of basal insulin (Ib) and the S_I index. GEZI is the difference between S_G and BIE: GEZI = $S_G - (S_I \cdot Ib)$.[26] Also, the model provides a variable, X(t), that represents the insulin action and is proportional to insulin in a "remote" compartment[25]; this compartment has been identified as the interstitium.[36,37]

Minimal Model of Insulin Kinetics

The minimal model of insulin kinetics (MMi) is the mathematical representation of plasma insulin when plasma glucose during a FSIGT is provided.[38] The estimation of MMi parameters was made in the same way as for MMg, using another personal computer program (STELLUM-MMi). MMi parameters permit us to calculate both Φ_1 and Φ_2 indices, which represent the relative responsiveness of first- and second-phase posthepatic insulin release to glucose stimulation, respectively.[38]

Calculations

An intravenous glucose tolerance index, K_G, was calculated as the slope of the least-squares regression line relating to the natural logarithm of glucose concentration to time between 8 and 40 minutes.

The apparent glucose distribution volume (V_D) was calculated as V_D = glucose dose/(G_0 − Gb), where glucose dose corresponds to the amount of glucose injected, Gb is basal glucose, and G_0 is glucose concentration at time zero assuming that glucose is mixed instantaneously in the extracellular fluid.[39]

Plasma insulin response to glucose was expressed as the insulin area under the curve (AUC) above basal between 0 and 10 minutes (first phase, $AUC_{0\text{-}10}$), between 22 and 90 minutes (second phase, $AUC_{20\text{-}90}$), and between 0 and 90 minutes (total response, $AUC_{0\text{-}90}$). All of these variables were calculated using the trapezoidal method.

Analytical Methods

Plasma glucose level was measured in triplicate using a Beckman Glucose Analyzer (Beckman Instruments, Palo Alto, CA) with a glucose oxidase method (intraassay and interassay coefficients of variation [CVs] <2%). Immunoreactive plasma insulin was estimated in duplicate by double-antibody radioimmunoassay.[40] Intraassay and interassay CVs were 6% and 11%, respectively. Plasma C-peptide concentrations were determined in duplicate using a radioimmunoassay method[41] (intraassay CV, 3.5%; interassay CV, 11%).

Statistical Analysis

Values are the mean ± SE. The accuracy of model parameters was evaluated by fractional standard deviation (FSD).[33] The FSD of GEZI was calculated by the δ method. Parameters with FSD values greater than 50% were rejected. Normality was checked using the Shapiro-Wilk

test. For comparisons, the paired Student's t test or Wilcoxon test were used as appropriate. Differences were considered statistically significant at P less than .05.

RESULTS

General characteristics of the subjects are shown in Table 1. Plasma glucose (FSIGTr v FSIGTe: 4.9 ± 0.2 v 5.1 ± 0.1 mmol · L^{-1}, nonsignificant [NS]), insulin (71 ± 7 v 73 ± 9 pmol · L^{-1}, NS), and C-peptide (0.506 ± 0.11 v 0.630 ± 0.10 nmol · L^{-1}, NS) levels at −1 minute were similar at rest and during exercise.

FSIGT

Plasma glucose, insulin, and C-peptide levels during FSIGT are illustrated in Fig 1. During the first 10 minutes, glycemia was significantly higher during exercise than at rest. However, from minute 20 until the end of the test, glycemia during exercise was significantly less than at rest. During physical exercise, intravenous glucose tolerance improved significantly, as indicated by a higher K_G index (2.19 ± 0.4 v 4.62 ± 0.2 min^{-1}, $P < .001$).

As expected, plasma insulin concentrations during exercise were significantly lower than at rest (Fig 1). The integrated insulin area above basal insulin was significantly less during exercise for the $AUC_{0\text{-}90}$ (21,000 ± 2,008 v 14,340 ± 2,596 pmol · L^{-1} · min, $P < .01$), $AUC_{0\text{-}10}$ (6,195 ± 903 v 4,617 ± 961 pmol · L^{-1} · min, $P < .05$) and $AUC_{22\text{-}90}$ (11,651 ± 1,427 v 6,381 ± 1,047 pmol · L^{-1} · min, $P < .03$).

Although C-peptide concentrations were also lower during exercise, we only found significant differences after 36 minutes of glucose injection (Fig 1).

MMg

During physical exercise, we found that the S_I index was significantly greater than at rest (8.5 ± 1.0 v 25.5 ± 7.2 × 10^{-5} · min^{-1} · pmol · L^{-1}, $P < .01$). The S_G index was also higher during exercise (Table 2). S_G index represents the normalizing effect of glucose per se at basal insulin on its own concentration in plasma independently of increased insulin. When we subtract the effect of basal insulin on this index (GEZI), the differences continue to be statistically significant (0.190 ± 0.03 v 0.269 ± 0.04 × 10^{-1} · min^{-1}, $P < .05$).

Table 1. General Characteristics of the Subjects

Subject No.	Sex/Age (yr)	Weight (kg)	Height (cm)	BMI (kg/m²)	$\dot{V}o_2max$ (mL/min)	Maximal Load (W)
1	F/26	59	167	21.2	1,950	110
2	F/20	62	167	22.3	2,500	150
3	F/32	63	158	25.3	1,804	130
4	M/25	70	187	20.0	2,950	190
5	M/29	69	182	20.8	2,950	180
6	F/29	51	148	23.3	1,236	96
7	F/26	51	159	20.1	2,100	140
8	M/42	69	185	20.1	2,840	190
9	F/25	60	162	22.8	1,300	120
10	F/30	53	147	24.5	2,000	140
11	M/61	80	175	26.2	1,900	130
12	M/36	77	175	25.0	2,500	140

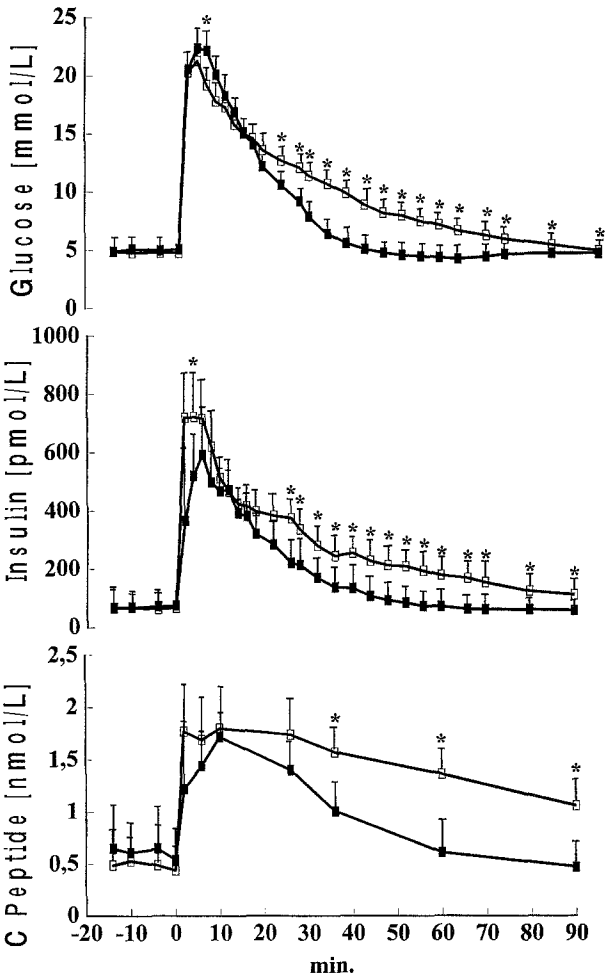

Fig 1. Plasma concentration profile for glucose, insulin, and C-peptide during a FSIGT test in 12 healthy subjects at rest (□) and during 95 minutes of physical exercise (■). Glucose load was administered at time zero (11.4 g/m²). *Statistically significant at $P < .05$.

In Fig 2, the values for the X(t) variable are shown during the FSIGTr and FSIGTe. This variable is proportional to the insulin concentration in the interstitium, and was significantly higher during exercise throughout practically the whole test.

MMi

Indices of the MMi are shown in Table 2. Both Φ_1 and Φ_2 indices were not statistically different at rest and during exercise.

DISCUSSION

Our results show, as has been widely reported,[7,16,18,21,42] that during physical exercise there is an improvement in glucose tolerance. This improvement is a consequence of a substantial increase in insulin sensitivity (300%) and in GEZI (142%), since the plasma level of the hormone was lower during exercise.

In this study, we used the abbreviated protocol for the minimal model to be sure that all subjects would finish the exercise bout. We did not use the tolbutamide protocol[43] for two

Table 2. Indices and Parameters of MMg and MMi

Index/Parameter	Rest	Exercise
S_I index ($\times 10^{-5} \cdot min^{-1} \cdot pmol \cdot L^{-1}$)	8.5 ± 1.0 (9 ± 7)	25.5 ± 7.2* (5 ± 4)
S_G index ($\times 10^{-1} \cdot min^{-1}$)	0.195 ± 0.03 (20 ± 9)	0.283 ± 0.03† (18 ± 11)
GEZI ($\times 10^{-1} \cdot min^{-1}$)	0.190 ± 0.03 (21 ± 8)	0.269 ± 0.04† (17 ± 13)
BIE (min^{-1})	0.005 ± 0.0002	0.014 ± 0.005†
Φ_1 index ($pmol \cdot L^{-1} \cdot min \cdot mmol \cdot L^{-1}$)	9.8 ± 2.3 (5 ± 5)	5.9 ± 1.5 (3 ± 2)
Φ_2 index ($pmol \cdot L^{-1} \cdot min^{-2} \cdot mmol \cdot l^{-1}$)	25.3 ± 6.2 (12 ± 7)	38.6 ± 9.8 (10 ± 8)
Glucose VD ($dL \cdot kg^{-1}$)	1.8 ± 0.2	1.3 ± 0.3†

NOTE. Values are the mean ± SE. Numbers in parentheses are data for FSDs of the parameters.

*$P < .01$.

†$P < .05$.

reasons: first, to avoid the risk of hypoglycemia when tolbutamide and exercise are combined, and second, to be able to use the MMi. In this respect, others[44,45] have used the standard protocol instead of the tolbutamide protocol for the second reason. On the other hand, although the reliability of measurements of minimal model parameters is clearly better with the tolbutamide protocol,[46] the FSDs of S_I and S_G were less than 30% in all cases studied; moreover, differences in the accuracy of these indices obtained with the glucose-only and the tolbutamide protocol[46] (27.8% *v* 9.7% for S_I, respectively) cannot justify the differences found in our study.

This study cannot deal with all the complexities of exercise and glucose metabolism (eg, HGO, ketogenesis, etc); however, the MMg is an accurate method to estimate insulin sensitivity and glucose effectiveness.

Others[22,27-30] have used Bergman's minimal model to study the effect of physical exercise on glucose metabolism. However, to our knowledge, no one has used this method during exercise. Nevertheless, an important concern of this study is that the minimal model has not been validated previously during such a highly non–steady-state condition as exercise. Thus, the important exercise-induced hemodynamic changes[47] could lead to a misinterpretation of the changes in minimal model indices. Although theoretically S_I, S_G, and GEZI indices are independent of glucose pool size and plasma glucose levels, which is true in a basal state, nevertheless, an important question is what happens to glucose V_D during exercise. Few reports have been published on this topic.[48] The minimal model assumes that glucose distribution can be described by a single compartment,[24] and because glucose is rapidly normalized during a FSIGT, the calculated V_D is similar to Steele's "pool fraction."[39] In this respect, exercise would normalize glucose even more rapidly. On the other hand, we do not know from our study if V_D remains constant or if it will change during the exercise bout. Concerning this, Finegood et al[48] found that during exercise in dogs, hepatic glucose production was similar when it was calculated using a one-compartment model with a fixed V_D or a one-compartment variable-pool model, and the average effective V_D estimated was also similar to the assumed volume with the fixed-pool model. In our study, V_D decreased during exercise, and this could underestimate both S_I and S_G indices, since plasma glucose during exercise is lower than at rest. These findings were a surprise, since we would have expected an increment in V_D during exercise, due to the opening of new capillaries in exercised muscles. Moreover, Finegood et al[48] found that glucose V_D was slightly enhanced during a 60-minute exercise bout. Others[49] have found that glucose V_D increases when cardiac output increases, although these studies were performed in seriously ill patients with different hemodynamic characteristics than those of exercise. The reasons for such a decrement in V_D during exercise are not clear. Catecholamine-induced splanchnic and renal vasoconstriction during exercise[47] could explain part of this finding. Another possible explanation is the exercise-induced water loss; however, this would assume a loss of about 3 kg, which is not the case. However, Wilkerson et al[50] found that plasma volume decreased as workload

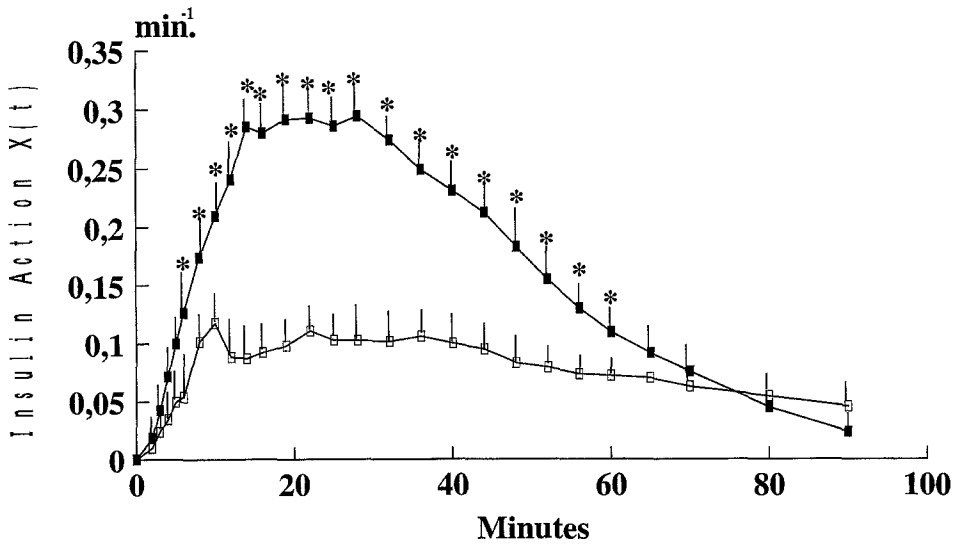

Fig 2. Time course for the variable X(t) from Bergman's MMg at rest (□) and during physical exercise (■). The variable X(t) represents insulin action and is proportional to lymph insulin. *$P < .05$.

increased, with minimal dehydration. Another possibility is that as we would expect a faster rate of glucose mixing into its space during exercise, the zero-weight scheme used during the fit could affect the V_D value; however, even assuming a faster glucose mixture, the V_D continues to be reduced during exercise. Despite this conundrum, taking into account that we were not estimating absolute glucose fluxes, that minimal model indices are independent of plasma glucose and insulin levels and glucose V_D, and, lastly, that our results agree in general terms with others obtained using different methodologies,[15,17] we believe this could be a valid approach to evaluate the relative proportions of glucose disposed of by insulin-dependent and non–insulin-dependent mechanisms during exercise.

The importance of insulin for glucose uptake during physical exercise has been reported in many studies.[15-17,42] Although it seems that the presence of insulin is not necessary for glucose uptake to increase during exercise,[11-13,18] the hormone would exert a synergistic effect rather than just an additive one.[15,17] With respect to the S_I index, our data show that during exercise it increases 300%. Using MMg after exercise, Brun et al,[30] Tokuyama et al,[22] and Kahn et al[28] have reported an increment of 183% after 25 minutes of physical activity[30] and of 150% and 36% after 16 and 60 hours of physical training, respectively. These results suggest that insulin sensitivity after exercise returns to baseline in a time-dependent way. It is important to emphasize that the S_I index also includes the effect of insulin to suppress HGO.[51] However, in the case of physical exercise, the increment of S_I must be mainly due to an increment in peripheral glucose uptake rather than to a suppression of HGO, since exercise increases HGO.[6,48]

GEZI also increased during exercise in our study. Wasserman et al[17] and Ahlborg et al[18] found that NIMGU represents the major part of the exercise-induced increment in glucose disposal. Other studies[22,30] using the minimal model but not all[27-29] have found that GEZI increases after physical exercise. Brun et al[30] found that 25 minutes after an exercise bout GEZI increased 160%, and this was the main component of the intravenous glucose tolerance exercise–induced increase, based on a stepwise multiple correlation. Although theoretically GEZI also includes the effect of glucose suppression of HGO, recent study[52] has shown that S_G is independent of the sensitivity of the liver to suppression by glucose; thus, variations in GEZI must reflect mainly modifications in NIMGU. Insulin sensitivity improves during and after exercise,[15,17,22,28,30] but the results for glucose effectiveness (or NIMGU) in different studies are not so constant. A plausible explanation is the different methodologies used in its calculation. Moreover, the S_G index is not as reliable an index as S_I,[53] and it could be influenced by diet[54] and the FSIGT protocol.[46] Furthermore, it has been recently demonstrated[55] that insulin and increased blood flow during exercise play an important role in glucose uptake, which might mask the effect of exercise on glucose effectiveness when calculated by MMg.

Despite the importance of NIMGU in exercise-induced glucose uptake shown by others,[17] in our study it seems that S_I plays a more important role than GEZI in peripheral glucose uptake, at least as a percentage. Others have indicated[11] that for NIMGU to take place during muscle contraction, muscle glycogen depletion is necessary. During a FSIGT, most of the glucose will be metabolized by muscle.[15,20,42] During exercise, muscle glycogenolysis will represent a small percentage as the energy source while there is blood-borne glucose; as glucose reaches the baseline and blood-borne substrate is reduced, muscular glycogenolysis will assume more importance and muscle glycogen content will decrease. This could explain the lesser increment observed in GEZI, since hyperglycemia and hyperinsulinemia persist during almost one third of the test.

In our study, we observed that the variable X(t) was significantly higher during exercise. It has been demonstrated that this variable is proportional to the lymph insulin concentration.[36,37] However, since this variable is $X(t) = (K_4 + K_6) \cdot$ interstitial insulin,[51] the increment in X(t) during exercise could be due to an increment in interstitial insulin alone, in $(K_4 + K_6)$ alone, or in both. Lymph insulin has been proposed as a good representation of insulin in the interstitium,[37] and in a recent study it was demonstrated that insulin exerts its action from this space.[56] On the other hand, during physical exercise, blood flow increases in the working muscles,[42,47] and Hespel et al[55] have demonstrated that, independently of the plasma insulin level, increased blood flow acts as a stimulus to glucose uptake in muscle. It has been hypothesized[7,10,15,57] that the opening of new capillaries during physical exercise increases insulin contact with muscle cells. Although the increment in X(t) during exercise could be due to an increment in $(K_4 + K_6)$ alone, and we have no way to confirm this, the increased blood flow[47,55] in exercised muscles leads us to postulate that during exercise the passage of insulin to the interstitium across the endothelium capillaries is more efficient despite the fact that during exercise plasma insulin concentration decreases. More studies will be necessary to confirm this fact.

We have found no differences in the Φ_1 and Φ_2 indices from the MMi either at rest or during physical exercise. These indices represent β-cell responsiveness to glucose during the first and second phases of insulin secretion, respectively. These results are consistent with those obtained by others.[28] Kahn et al[28] have studied the mechanism responsible for the decrease in insulin secretion after exercise using the insulin response to arginine infusion. They found that the β-cell secretory response decreased after exercise while β-cell responsiveness to glucose was unaltered.

In summary, during moderate physical exercise, there is a significant increment in insulin sensitivity and GEZI. The higher glucose uptake is mainly insulin-mediated, and in a lower proportion, non–insulin-mediated, during a FSIGT test. Moreover, exercise seems not to modify β-cell sensitivity to glucose. Finally, the higher levels for the variable X(t) during exercise indirectly suggest a greater insulin passage across capillaries to the interstitium, despite its lower levels in plasma.

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